

these patients remain asymptomatic, and left sided pleural or pulmonary nodules may be discovered many years after the episode of trauma. Pulmonary nodules are often malignant, and it is commonly accepted that they should be considered malignant unless proven otherwise. Alertness to the possibility of thoracic splenosis can lead to confirmation of the diagnosis by the use of radionuclide scanning, and so prevent unnecessary thoracotomy and rendering the patient asplenic.

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Effects of nedocromil sodium in the treatment of non-allergic subjects with chronic obstructive pulmonary disease

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Abstract

Background – Nedocromil sodium, a non-steroidal anti-inflammatory drug, is effective in the treatment of asthma. Its efficacy in the treatment of chronic obstructive pulmonary disease (COPD) has not been investigated.

Methods – Fifty four non-allergic patients with COPD were randomised to 10 weeks of treatment with placebo or nedocromil sodium (4×8 mg/day) in a double blind study.

Results – Nedocromil sodium treatment had no effect on airway responsiveness to histamine, methacholine, and adenosine-5'-monophosphate, pulmonary function, and symptom scores. Both patients and clinicians favoured treatment with nedocromil sodium, however, and the number of dropouts (because of exacerbations) was fewer during treatment with the drug. **Conclusions** – Longer trials will be necessary to assess if nedocromil sodium can reduce the frequency of exacerbations and the decrease in pulmonary function, eventually leading to a better quality of life in patients with COPD.

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Nedocromil sodium has been shown to be effective in the treatment of patients with al-

lergic asthma.¹ Studies investigating its effects in chronic obstructive pulmonary disease (COPD) are not available. The aim of our study was to investigate the effects of 10 weeks of treatment with nedocromil sodium on airway responsiveness to histamine, methacholine, and adenosine-5'-monophosphate (AMP), pulmonary function, and clinical symptoms in a group of non-allergic patients with COPD. As anti-inflammatory treatment in COPD is generally accompanied by little or no change in clinical parameters a high dose of nedocromil sodium (arbitrarily determined at 32 mg daily) was chosen.

Methods

SUBJECTS

All participants were at least 40 years of age and had a diagnosis of COPD based on the recommendations of the American Thoracic Society,² meeting the following criteria: (1) no atopy: negative skin reactions to 18 common aeroallergens, negative specific serum immunoglobulin E to house dust mite, and peripheral blood eosinophils $<450/\text{mm}^3$; (2) forced expiratory volume in one second (FEV_{10}) >1 litre and $<70\%$ predicted and FEV_{10} after $40 \mu\text{g}$ ipratropium bromide $<80\%$ predicted; (3) concentration of histamine causing a 20% decrease

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Mean (SD) characteristics of patients

	Placebo (n = 21)	Nedocromil sodium (n = 27)
Gender (M/F)	18/3	26/1
Age (years)	61.2 (1.8)	60.4 (1.5)
Smokers (n)	10	15
Cigarettes/day	8.0 (2.5)	6.9 (1.7)
Pack years	22.6 (3.2)	20.7 (2.3)
Eosinophils/mm ³	147.0 (28.9)	136.5 (16.5)
Reversibility*	8.4 (1.2)	6.3 (0.8)
FEV ₁ (% predicted)	49.2 (2.5)	50.6 (2.2)
IVC (% predicted)	83.8 (2.9)	80.8 (2.4)
PC ₂₀ histamine**	0.2	0.2
PC ₂₀ methacholine**	0.4	0.4

FEV₁ = forced expiratory volume in one second; IVC = inspiratory slow vital capacity.

* Reversibility expressed as Δ FEV₁ (% predicted). ** Geometric mean (mg/ml).

of FEV₁ from baseline (PC₂₀) <8 mg/ml; (4) no upper respiratory tract infection or exacerbation during six weeks before the start of the study. Patients with asthmatic attacks and wheeze were excluded. The study was approved by the hospital medical ethics committee and all subjects gave their written informed consent.

STUDY DESIGN

The study comprised a two week single blind placebo baseline, a 10 week double blind active treatment, and a 2 week placebo washout period. Inhaled corticosteroids were stopped two weeks before the start of the study. During the study only bronchodilators were allowed, but were discontinued eight hours before each clinic visit. Nedocromil sodium (2 mg/puff) or placebo were given as four inhalations four times daily via a Nebuhaler. At each two week visit lung function (FEV₁ and inspiratory slow vital capacity (IVC)) was measured with a calibrated water sealed spirometer, and cumulative dose-response histamine and methacholine inhalation provocation tests were performed. Similarly, AMP inhalation provocation tests were performed just before and at the end of the treatment period.³ All patients kept a daily diary card using a four point severity scale (0 = no symptoms, 3 = very severe symp-

toms) to assess both day and night time dyspnoea scores, cough severity, sputum production, additional bronchodilator medication, and the highest of three measurements of morning and evening peak expiratory flow (PEF) using the mini-Wright peak flow meter.

DATA ANALYSIS

All PC₂₀ values were analysed after base 2 logarithmic transformation, one log unit being one dose step in concentration. Comparisons of the effects of nedocromil sodium and placebo were made on changes from baseline and the mean treatment effects were calculated from the final eight weeks of the 10 week double blind treatment period, taking into account at least four weeks of treatment. The clinical effects of placebo and nedocromil sodium on pulmonary function, airway responsiveness, and symptom scores were assessed by Student's *t* tests for grouped values or Mann-Whitney U tests as appropriate. A survival analysis (Kaplan-Meier with the Mantel-Cox statistic) was performed to compare treatments using the number of days on treatment before withdrawal. Two tailed tests have been used throughout at the 95% level of significance.

Results

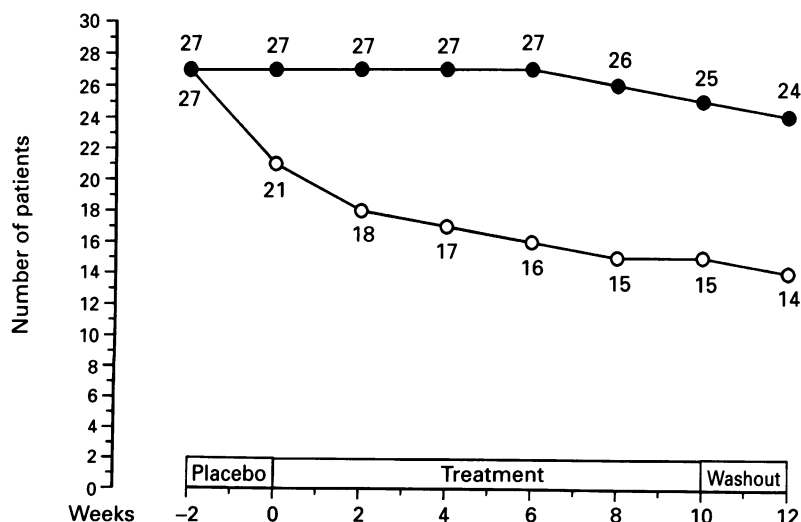
Fifty four patients with COPD entered the study and were randomised to treatment; six patients dropped out during the baseline period and were excluded from treatment analysis. Twenty one patients started treatment with placebo and 27 with nedocromil sodium (table). Fifteen patients in the placebo group and 21 in the treatment group were taking inhaled corticosteroids before the study (mean daily dose <700 µg in each group (*p*>0.05)). Six patients withdrew during placebo administration and two during nedocromil sodium (*p*<0.05). During the washout period one patient was withdrawn after placebo and one after nedocromil sodium, all because of an exacerbation of their airways disease (figure).

FEV₁ (% predicted), morning PEF, evening PEF, diurnal peak flow variation, PC₂₀ histamine, PC₂₀ methacholine, PC₂₀AMP, and all diary card symptom scores were similar for both placebo and nedocromil sodium groups. Taking use of corticosteroids before the treatment as covariable, there was no significant effect on these parameters.

Treatment was considered at least slightly effective in 59% of the patients receiving nedocromil sodium and in 43% of those receiving placebo (*p*>0.05), whereas the clinician (JW de J) considered the treatment at least slightly effective in 63% of those on nedocromil sodium and 24% of those on placebo (*p*<0.01). Side effects during nedocromil sodium and placebo were negligible.

Discussion

This is the first study to investigate the effects of nedocromil sodium in non-allergic patients with COPD. Following 10 weeks of treatment



Number of patients during the double blind randomised, placebo controlled study (● = nedocromil sodium, ○ = placebo). During the washout period all patients received placebo.

with nedocromil sodium and placebo there were only two treatment differences in favour of nedocromil sodium: the rate of withdrawals, all due to exacerbations, was significantly lower during treatment with nedocromil sodium, whereas clinician opinion of treatment efficacy significantly favoured nedocromil sodium.

There are several explanations why treatment with nedocromil sodium in our patients with COPD failed to improve clinical parameters. It is possible that nedocromil sodium is not a potent anti-inflammatory agent in this patient group; however, if nedocromil sodium is effective the duration of treatment may have been too short, as has been suggested for other anti-inflammatory agents.⁴ The type of airway inflammation, which is different in asthmatics⁵ who generally respond better to anti-inflammatory medication,⁶ may also play a part. Instead of symptom scores, lung function, and airway responsiveness, other clinical parameters such as quality of life, decline in pulmonary function, or number and duration of exacerbations may be necessary to measure treatment efficacy in COPD.⁷ In this perspective our patients showed, in the short period of follow up, significantly fewer exacerbations when treated with nedocromil sodium. However, at the expense of treatment with nedocromil sodium, the higher withdrawal rate in the placebo group leads to selection bias, thus underestimating differences between placebo and nedocromil sodium treatment.

In conclusion, 10 weeks of treatment with a high daily dosage of nedocromil sodium did not improve pulmonary function, airway responsiveness, and clinical symptoms. The number of withdrawals, all due to exacerbations, was significantly greater in the placebo group than in the nedocromil sodium group. Longer trials will be necessary to determine whether nedocromil sodium reduces the frequency of exacerbations and the decrease in pulmonary function, eventually leading to a better quality of life in patients with COPD.

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Effect of inhaled menthol on citric acid induced cough in normal subjects

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Abstract

Background - Menthol is a commonly used ingredient in many over the counter cough remedies, but there is little objective evidence as to its efficacy.

Methods - Twenty healthy subjects received a cough challenge consisting of five inhalations of 33 µmol citric acid from an air driven dosimeter. The challenge was repeated at hourly intervals for five hours. Five minutes before each challenge subjects inhaled, in a randomised design, either menthol 75% in eucalyptus oil or one of two placebos (pine oil or air).

Results - Menthol inhalation caused a reduction in evoked cough when compared with either placebo.

Conclusions - Menthol is an effective antitussive agent in an evoked cough model.

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L-Menthol, a volatile aromatic compound, is the principal component of the essential oil derived from peppermint (*Mentha piperita*). L-Menthol and the synthetic racemate DL-menthol are included in a number of proprietary medicines sold for the treatment of symptoms due to the common cold.

In this study we have investigated the effect of menthol inhalation in a citric acid induced cough model and compared its effects with that of two placebo treatments, the first an inhaler